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(54) Title: PROCESS FOR THE PREPARATION OF STANOL ESTERS

(57) **Abstract**

The invention relates to a process for the preparation of stanol esters by hydrogenating a sterol blend in a hydrogenation solvent and at an elevated temperature in the presence of a hydrogenation catalyst, by removing the hydrogenation catalyst from the obtained hot reaction solution, by transesterifying the intermediate stanol blend with a fatty acid methyl ester at an elevated temperature and in the presence of a transesterification catalyst, and by finally purifying the stanol ester blend thus obtained. According to the invention, the intermediate stanol blend is neither crystallized nor removed from the reaction solution but the hydrogenation solvent is replaced therein at least in part by a transesterification reagent. Alternatively, the hydrogenation solvent may also be used as the transesterifacation solvent, and preferably also as the transesterification reagent.

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Process for the preparation of stanol esters

The present invention relates to a process for the preparation of stanol esters, and in particular to a process wherein stanol esters are prepared by hydrogenating at least one sterol in a solvent and at an elevated temperature in the presence of a hydrogenation catalyst to the corresponding stanol or stanol blend, by removing the hydrogenation catalyst from the obtained reaction solution, by transesterifying the stanol or the stanol blend with a lower alkyl ester at an elevated temperature and in the presence of a transesterification catalyst, and by finally purifying the stanol ester or stanol ester blend thus obtained.

Sterols are compounds commonly present in plants and animals, although in small concentrations. The sterol compound most commonly present in animals is cholesterol. The sterol material present in plants is usually composed of several sterol structures which resemble each other structurally. The most common of the latter are β-sitosterol, campesterol and stigmasterol. Depending on the plant species, there may also be present numerous other compounds resembling the above-mentioned sterols, for example brassicasterol in rape, α-sitosterol and betulinol in birch, methylene cycloartanol and cycloartenol, avenasterols, etc.

The sterols of wood material also include saturated sterol compounds wherein particularly the double bond between carbon atoms 5 and 6 of the sterol structure is hydrogenated to a saturated carbon-carbon bond. These compounds are called stanols. The stanol corresponding to the most common plant sterol, β-sitosterol, is thus β-sitostanol. Hydrogenation of sterols is described e.g. in Organic Preparations and Procedures 1 (2) (1969) 107-109 (Augustine, R.L. and Reardon Jr. E.J.: The Palladium catalyzed hydrogenation of cholesterol) and Atherosclerosis 24 (1975) 301-309 (Sugano, M. et al.: Lipid-lowering activity of phytosterols in rats).

Cholesterol is a compound indispensable for human subjects, as for other vertebrates, for example as an ingredient of cell structures. In high concentrations, however, cholesterol is detrimental, since it accumulates on the walls of blood vessels and thereby increases the risk of cardiovascular diseases.

It has been observed in investigations that plant sterol compounds, and in particular plant stanol compounds, added to the diet lower the blood serum cholesterol concentration in human subjects. When it is desired to use compounds derived from

catalyst has been removed, and thereafter the hydrogenation solvent is removed by distillation before the actual transesterification. The use of fatty acid methyl esters can, however, be justified, since they have a higher flash point than have conventional solvents, such as n-propanol, which means improved fire safety.

The hydrogenation catalyst used is preferably a noble metal catalyst, such as palladium on carbon or on an organic polymer compound. The hydrogenation is preferably carried out at a temperature of at most about 120 °C, but the hydrogen pressure may vary in a wide range. Also the amount of the hydrogenation catalyst used in the reaction may vary, but may preferably be used in an amount of 0,1-2 % active ingredient of the weight of the sterol to be hydrogenated. By this selection of hydrogenation conditions, the hydrogenation can be carried out at a high concentration of solids, rapidly, and without the formation of detrimental degradation products.

At the end of the hydrogenation reaction, the hydrogenation catalyst is removed by filtration from the hot reaction mixture. The filtration of the hydrogenation catalyst is problem-free and does not require high investments.

The transesterification catalyst used is preferably an alkali metal alcoholate, such as sodium methylate or sodium ethylate. In this case the amount of transesterification catalyst is preferably 0.1-1 % of the weight of the reaction solution.

The transesterification is preferably carried out at 100-130 °C and by using a stoichiometric excess of the transesterification reagent, for example a double excess, relative to the stanol or the stanol blend.

In the process according to the invention, the starting substance used may be any sterol or sterol blend obtainable from plants, and in principle also animal sterols, for example cholesterol or lanosterol. Preferably, however, a sterol blend is hydrogenated which contains mainly sitosterol and additionally campesterol and possibly stigmasterol. Especially preferably, a sterol blend based on tall oil or vegetable oil is hydrogenated.

It has now been shown, surprisingly, that even if the crystallization of the stanol intermediate and the removal of the crystals by filtration, regarded as indispensable in the prior known method for the preparation of stanol esters, are omitted, the stanol ester end product can, however, be recovered in a sufficiently pure state and,

above all, with a higher yield, by using after the transesterification step purification processes known per se. Even if the concentration of impurities (e.g. dehydrogenation products of tocopherols and sterols, long-chained hydrocarbons, and fatty alcohols) formed in the reaction and brought in by the raw materials were rather high, their removal by the method according to the invention is possible by using, for example, steam distillation and adsorption, known per se. In addition to these purification procedures, for example, thin film evaporation can also be used.

Detailed description of the invention

In the first step of the reaction series, the hydrogenation, it is preferable to use as catalyst a noble metal catalyst such as palladium, platinum or ruthenium. Also possible is, for example, Raney nickel, cobalt, or copper chromite compounds. The catalyst support may be, for example, carbon, alumina, silica gel, or an organic polymeric compound.

The hydrogenation is most preferably carried out at a temperature below about 120 °C. The pressure in the reaction mixture may vary widely. The catalyst concentration may also vary within a wide range. By keeping the temperature about the above mentioned level the formation of by-products (e.g. splitting off reactions of hydroxyl) is most effectively avoided.

By an appropriate selection of the hydrogenation conditions, a situation is thus arrived at wherein the hydrogenation can be carried out at a high solids concentration, rapidly, and without the formation of detrimental degradation products.

When the hydrogenation reaction has been brought to completion, the hydrogenation catalyst is removed from the hot reaction mixture by filtration.

If the removal of a portion of the hydrogenation solvent (methyl ester or some other solvent) is desired before the transesterification, it must be done in the subsequent step. This is done by adding the fatty acid methyl ester to be used in the transesterification to the hydrogenation reaction mixture before the distillation or simultaneously with the distillation. The conditions used in the distillation of the solvent are, of course, dependent on the physical properties of the solvent used. It is, however, a marginal condition that the boiling point of the hydrogenation solvent must deviate sufficiently (must be lower) from the boiling point of the fatty acid

ester serving as the reagent, in order for fractional removal of the hydrogenation solvent to be possible.

The next step in the preparation of stanol ester is the transesterification of the stanol with the fatty acid ester contained in the reaction solution.

The esterification reaction per se may take place under the effect of any reagent catalyzing transesterification (examples include inorganic acids, toluene sulfonic acids, organostannates or alkaline catalysts). However, it is especially preferable to use in the transesterification alkali metal alcoholates, for example, sodium methylate or sodium ethylate, transesterification catalysts well known per se from the literature in the field. The catalyst concentration and the other reaction conditions required vary largely as a function of the type of catalyst used. In a reaction occurring under the effect of sodium methylate it is preferable to use the catalyst in an amount of approx. 0.1-1 % of the amount of the reaction mixture. The temperature being approx. 100-130 °C, the reaction occurs completely within approx. 60-180 min when an approx. double stoichiometric excess of the fatty acid methyl ester relative to the stanol amount is used in the transesterification.

After the reaction step, the impurities formed in the reaction and brought in with the raw material (catalysts, sterol degradation products, etc.) can be removed by means of water washes and by water vapor distillation and additionally, when necessary, by causing the impurities to be absorbed into a suitable absorbent material (examples include activated carbon and/or bleaching earth). Steam distillation is a necessary purification step also for the removal of any reagent excess. Suitable conditions in the steam distillation step, when the reagent is the methyl ester of rapeseed fatty acids, are: temperature 180-230 °C, pressure 1-10 mbar, and the amount of steam to be fed approx. 2-10 % of the total amount of the reaction mixture.

Examples on the preparation of stanol esters according to the invention are presented below.

Example 1

300 g of a sterol derived from tall oil (10 % campesterol/stanol, 90 % β-sitosterol/stanol) was slurried into 700 g of coconut fatty acid methyl ester (which contains primarily C_6-C_{14} fatty acid esters). A Pd catalyst bound to polypropylene

fiber, Smop-20 (manufacturer Smoptech, Turku, Finland), was added in an amount of 0.7 % of the amount of sterol, the temperature was raised to 120 °C, and the reaction autoclave was rinsed with nitrogen. Thereafter hydrogen was directed to the reaction mixture for 130 min. During the hydrogenation the pressure of the reaction mixture varied within a range of 1-2 atm. The hydrogenation catalyst was removed by distillation from the hot reaction mixture. Thereafter 360 g of rapeseed oil fatty acid methyl ester was directed to the reaction mixture, and the coconut methyl ester which had served as a solvent was removed by distillation at a temperature of 140 °C and a pressure of 8 mbar. Thereafter 3 g of sodium methylate was added as an esterification catalyst, and the esterification reaction was allowed to occur at 120 °C for 1.5 h at a pressure of 5 mbar. The ester product was washed twice with water, and the excess methyl ester reagent and impurities were steam distilled at a temperature of 200 °C and a pressure of 3 mbar. The product was filtered while hot through bleaching earth and a layer of activated carbon. The stanol ester product contained free fatty acids 0.02 %, fatty acid methyl esters 0.3 %, and unesterified sterol-derived compounds 0.8 %. The melting point of the stanol ester was 36-39 °C according to DSC determination.

Example 2

295 g of a sterol derived from vegetable oil (25 % campesterol, 55 % β-sitosterol and 15 % stigmasterol) was slurried into 705 g of coconut fatty acid methyl ester (which contains primarily C_6-C_{14} fatty acid esters). A Pd/C catalyst was added (5 % Pd on a carbon support, 0.2 % palladium of the amount of sterol), the temperature was raised to 120 °C, and the reaction autoclave was rinsed with nitrogen. After the nitrogen had first been replaced by a hydrogen atmosphere, hydrogen was directed to the reaction mixture for 110 min. During the hydrogenation the pressure of the reaction mixture was 1-2 atm.

The hydrogenation catalyst was removed from the hot reaction mixture by filtration.

Thereafter 3 g of sodium methylate was added as the esterification catalyst, and the esterification reaction was allowed to occur at a temperature of 125 °C for 1.5 h at a pressure of 5 mbar, whereby the formed methanol was at the same time removed. The ester product was washed twice with water, and the excess methyl ester reagent and impurities were steam distilled first at a temperature of 140-145 °C and a pressure of 7-9 mbar. Finally the temperature was raised to 200-205 °C (pressure 3-4 mbar) in order to remove the higher boiling impurities. The product was filtered

while hot through bleaching earth and a layer of activated carbon. The stanol ester product contained free fatty acids 0.025 %, fatty acid methyl esters 0.3 %, and unesterified sterol-derived products 0.6 %. The melting point of the stanol ester was 93-97 °C according to DSC determination.

Example 3

In a process according to Example 2, rapeseed oil methyl ester was used as the hydrogenation solvent and at the same time as the esterification reagent instead of coconut fat methyl ester. The reaction and the purification steps were carried out as in Example 2 (however, the temperature and pressure were 200-205 °C/3-4 mbar throughout the steam distillation). The product obtained was a wax having a melting range of 98-104 °C.

Example 4

In this example, the hydrogenation solvent used was coconut fatty acid methyl ester, which was partly removed by distillation and replaced with rapeseed oil methyl ester before the transesterification.

250 g of a sterol derived from vegetable oil was slurried into 650 g of coconut fatty acid methyl ester. A Pd/C catalyst was added in an amount of 0.2 %, and the sterol was hydrogenated as in the preceding examples.

The hydrogenation catalyst was removed from the hot reaction mixture by filtration.

Thereafter, 300 g of rapeseed oil methyl ester was added to the reaction mixture, and 300 g of the saturated coconut fatty acid ester was distilled at a temperature of 140-150 °C and a pressure of 7-9 mbar. The mixture was transesterified and purified in the manner described in the preceding examples. The reaction product was a light yellow wax having a melting range of 69-74 °C.

Example 5

In the process according to Example 1, a high boiling (distillation range 180-210 °C) aliphatic hydrocarbon free of aromatic compounds was used as the hydrogenation solvent instead of coconut fatty acid ester. The reactions and purification processes were carried out substantially in the manner described in

Example 1. The reaction product obtained was a wax corresponding to the product of Example of 1 and having a melting range of 37-40 °C.

Claims

1. A process for the preparation of stanol esters by hydrogenating at least one sterol in a solvent and at an elevated temperature in the presence of a hydrogenation catalyst, to form respectively at least one stanol, by removing the hydrogenation catalyst from the obtained reaction solution, by transesterifying the said at least one stanol with a lower alkyl ester at an elevated temperature and in the presence of a transesterification catalyst, and by purifying the stanol ester or stanol ester blend thus obtained, **characterized** in that the hydrogenation solvent is left in the reaction solution from which the hydrogenation catalyst has been removed, and the hydrogenation solvent

a) is replaced therein at least in part by a transesterification reagent and/or

b) is used as a solvent also in the transesterification and preferably at the same time as the transesterification reagent.

2. A process according to Claim 1, **characterized** in that a fatty acid methyl ester of vegetable oil origin is used as the transesterification reagent and possibly as the hydrogenation solvent.

3. A process according to Claim 2, **characterized** in that the hydrogenation solvent is lower boiling than the transesterification reagent and is removed by fractional distillation from the reaction solution, to which a transesterification reagent is added or has been added.

4. A process according to Claim 3, **characterized** in that a coconut fatty acid methyl ester is used as the hydrogenation solvent and a rapeseed oil fatty acid methyl ester as the transesterification reagent.

5. A process according to Claim 1, **characterized** in that an alcohol or a high boiling aliphatic hydrocarbon free of aromatic compounds is used as the hydrogenation solvent and at the same time as the transesterification solvent.

6. A process according to any of the above claims, **characterized** in that a noble metal catalyst, preferably palladium on carbon or on an organic polymer compound, is used as the hydrogenation catalyst.

7. A process according to Claim 6, **characterized** in that the hydrogen catalyst is used in an amount of 0.1-2 % active ingredient of the weight of the sterol to be hydrogenated.

8. A process according to any of the above claims, **characterized** in that the hydrogenation is carried out at a temperature of at most about 120 °C, and the hydrogenation catalyst is removed from the hot reaction solution, preferably by filtration.

9. A process according to any of the above claims, **characterized** in that an alkali metal alcoholate, preferably sodium methylate or sodium ethylate, is used as the transesterification catalyst.

10. A process according to Claim 9, **characterized** in that the transesterification catalyst is used in an amount of 0.1-1 % of the weight of the reaction solution.

11. A process according to any of the above claims, **characterized** in that the transesterification is carried out at 100-130 °C and by using a stoichiometric excess of the transesterification catalyst relative to the stanol or the stanol blend.

12. A process according to any of the above claims, **characterized** in that a sterol blend is hydrogenated which contains primarily sitosterol and additionally campesterol and possibly stigmasterol.

13. A process according to Claim 12, **characterized** in that a sterol blend based on tall oil or vegetable oil is hydrogenated.

INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07J 9/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9219640 A1 (RAISION MARGARIINI OY), 12 November 1992 (12.11.92) --	1-13
A	US 4428885 A (YUZO HIGAKI ET AL), 31 January 1984 (31.01.84) --	1-13
P,A	WO 9801126 A2 (UNILEVER N.V.), 15 January 1998 (15.01.98) --	1-13
P,A	WO 9806405 A1 (RAISION TEHTAAT OY AB), 19 February 1998 (19.02.98) -- --------	1-13

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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